

Supplemental Information

Supplemental Figures and Figure Legends

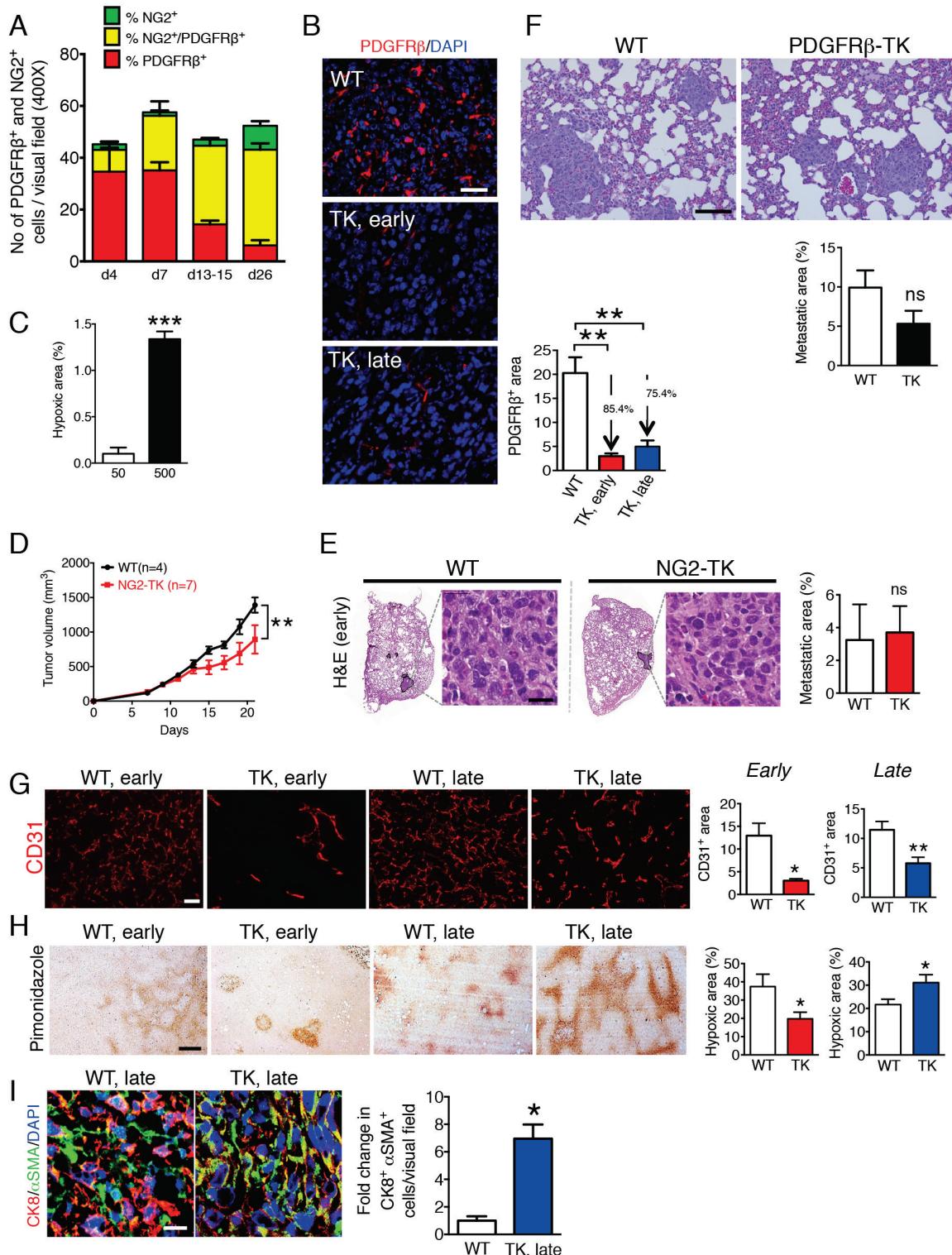


Figure S1. PDGFR β^+ and NG2 $^+$ pericyte recruitment in 4T1 tumor progression, related to**Figure 1.**

A Number of NG2 $^+$, PDGFR β^+ , and NG2 $^+$ /PDGFR β^+ double positive cells per field of view. d4, n=3; d7, n=3; d13-15, n=3; d26, n=5. **B** Representative images of tumors immunolabeled for PDGFR β and quantification of the relative PDGFR β^+ area in tumors with late (blue) and early (red) PDGFR β^+ pericyte depletion. WT, n=8; PDGFR β -TK early, n=5; PDGFR β -TK late, n=4. Scale bar: 50 μ m. Percentage differences in PDGFR β^+ areas are listed relative to the WT group.

C Percent hypoxic area in 50 and 500mm 3 4T1 orthotopic tumors. 50mm 3 , n=3; 500mm 3 , n=3. **D** Tumor volume measurements over time in mice with NG2 $^+$ pericytes depletion beginning at an early stage of tumor progression. GCV treatment started before total tumor burden reached 100 mm 3 . Two-way ANNOVA with Bonferroni's multiple comparison test was used. **E** H&E staining of lungs from the indicated experimental groups and quantification of the percent lung metastatic area. WT, n=4; NG2-TK, n=5. The metastatic nodules are encircled. High-magnification images of metastatic nodules are shown, scale bar: 25 μ m. **F** H&E staining of lungs from wild-type (WT) and PDGFR β -TK mice following 4T1 intravenous injection and respective quantification of the percent lung metastatic area. WT, n=8; PDGFR β -TK, n=8. Scale bar: 100 μ m. **G** Representative image of tumors immunolabeled for CD31 and quantification of the percent CD31 $^+$ area per field of view. WT early, n=4; PDGFR β -TK early, n=4; WT late, n=6; PDGFR β -TK late, n=6. Scale bar: 50 μ m. **H** Representative images of tumors immunolabeled for pimonidazole adduct formation (hypoxic area) in the indicated experimental groups and quantitation of the percent hypoxic area. WT early, n=7; PDGFR β -TK early, n=8; WT late, n=10; PDGFR β -TK late, n=14. Scale bar: 250 μ m. **I** Representative images of tumors immunolabeled for CK8 and α SMA in the indicated experimental groups and quantification of

the relative CK8⁺αSMA⁺ cells per visual field. WT, n=3; PDGFRβ-TK, n=3. Scale bar: 10 μm.

Different images for this experiment are also shown in Figure 4G. Data are represented as the mean +/- SEM. Unless otherwise noted, unpaired two-tailed t-test was used to determine statistical significance. * p<0.05, ** p<0.01. ns: not significant.

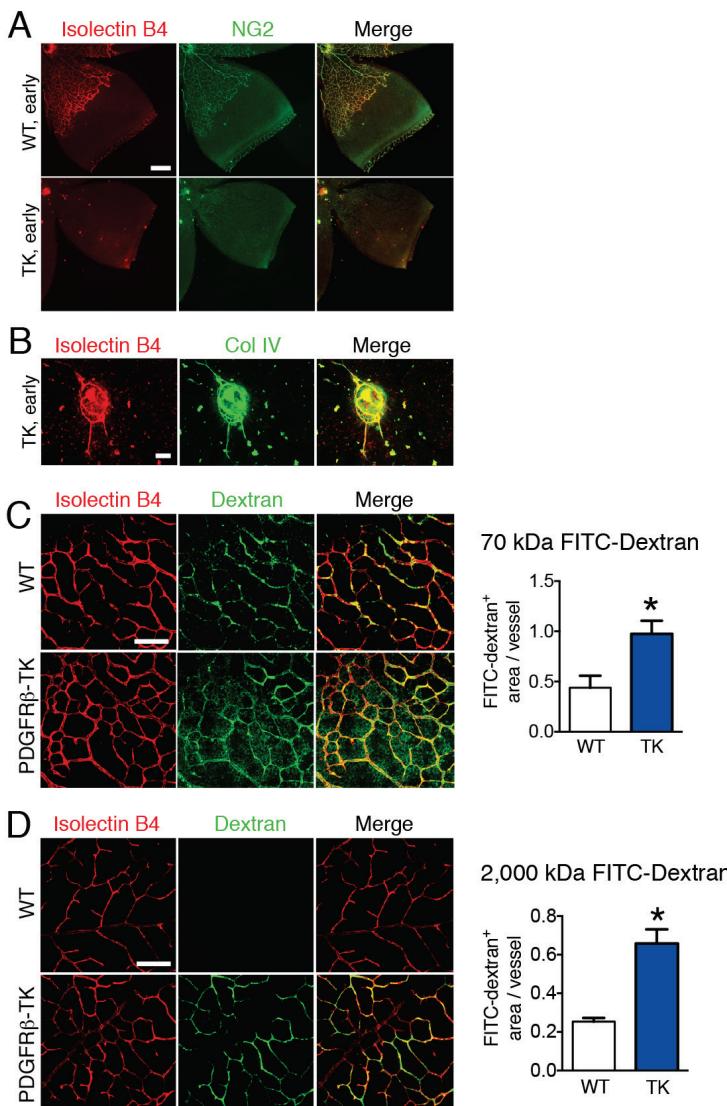


Figure S2. Vascular phenotype in retina angiogenesis with PDGFR β^+ pericyte depletion, related to Figure 2.

A Immunolabeling for NG2 (pericytes marker) and Isolectin B4 staining in retina of WT and PDGFR β -TK mice treated with GCV from P0 to P5 (early depletion) or from P4 to P9 (late depletion). Scale bar: 500 μ m. **B** Immunolabeling for Collagen IV followed by Isolectin B4 staining of retinas from PDGFR β -TK mice treated with GCV from P0 to P5. Scale bar: 100 μ m.

C Isolectin B4 staining and visualization of 70 kDa FITC-dextran in retina of WT and PDGFR β -TK mice treated with GCV from P4 to P9 and quantitation of FITC-dextran $^+$ area per vessel. Scale bar: 100 μ m. WT, n=3; PDGFR β -TK, n=5. These data are also shown in Figure 2G. **D** Isolectin B4 staining and visualization of 2,000 kDa FITC-dextran in retina of WT and PDGFR β -TK mice treated with GCV from P4 to P9 and quantitation of FITC-dextran $^+$ vessel. Scale bar: 100 μ m. WT, n=3; PDGFR β -TK, n=3. Data are represented as the mean +/- SEM. Unpaired two-tailed t-test was used to determine statistical significance. * p<0.05.

A

Rank	TK vs. WT, early ablation	TK vs. WT, late ablation
1	Relaxin signaling	IGF-1 signaling
2	Angiopoietin signaling	VEGF signaling
3	Growth hormone signaling	Growth hormone signaling
4	VEGF signaling	GM-CSF signaling
5	PDGF signaling	EGF signaling
6	HGF signaling	Angiopoietin signaling
7	GM-CSF signaling	PDGF signaling
8	IGF-1 signaling	VEGF family ligand-receptor interactions
9	VEGF family ligand-receptor interactions	Erythropoietin signaling
10	Erythropoietin signaling	HGF signaling

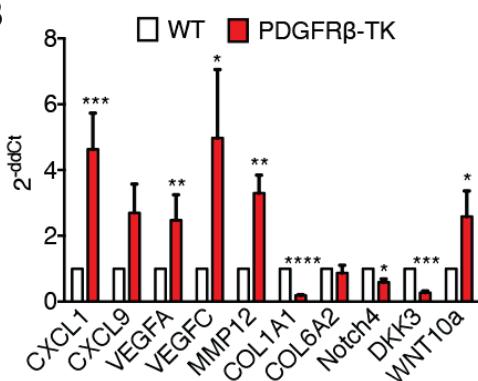
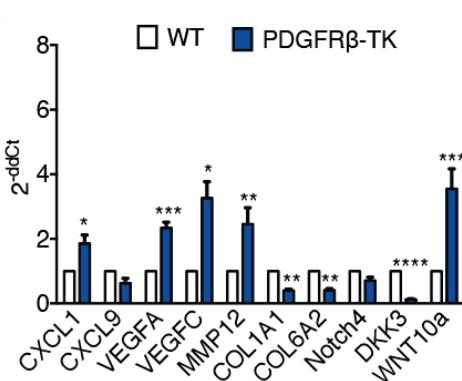
B**C**

Figure S3. Pathway analyses from global gene expression profiling and qRT-PCRs of differentially expressed genes in 4T1 tumors with early vs. late pericyte depletion, related to Figure 3.

A Ranked list of top 10 growth factor signaling pathways based on the differentially expressed genes in 4T1 tumors from WT vs. PDGFR β -TK mice with pericyte depletion in the early and late setting. **B-C** Transcript levels for the indicated genes assayed by quantitative RT-PCR in 4T1 tumors from WT and PDGFR β -TK with early pericyte depletion (B) and late pericyte depletion (C). Data are represented as the mean +/- SEM. n > 3 in all groups was used. The control group (WT) was arbitrarily set to 1, unpaired one-tailed t-test. * p<0.05, ** p<0.01, *** p<0.001, ****p < 0.0001.

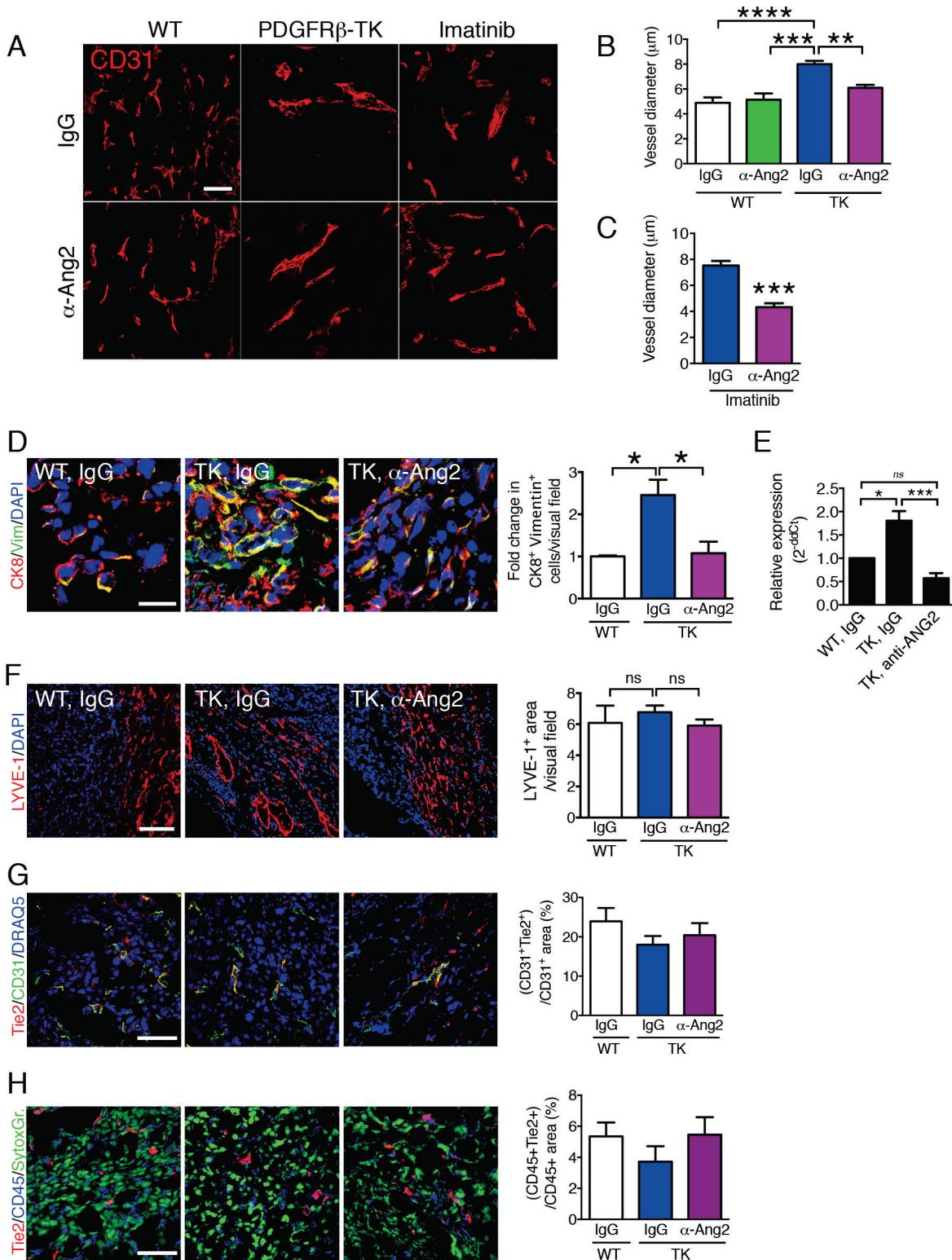


Figure S4. Anti-Ang2 antibody treatment restores vessel diameter in pericyte depleted tumors and suppresses EMT, related to Figure 4.

A Immunolabeling for CD31 in the tumors of the indicated experimental groups. Scale bar: 50 μm . **B-C** Quantification of the mean vessel diameter. B: IgG + WT, n=4; anti-ANG2 + WT, n=3; IgG + PDGFR β -TK, n=5; anti-ANG2 + PDGFR β -TK, n=5. One-way ANOVA with Tukey post-hoc analysis. C: IgG + Imatinib, n=4; anti-ANG2 + Imatinib, n=4. Unpaired two-tailed t-test. **D** Representative images of tumors immunolabeled for CK8 and Vimentin (Vim) in the indicated experimental groups and quantification of the relative CK8 $^+$ Vim $^+$ cells per visual field. WT, n=3; PDGFR β -TK, n=4; anti-ANG2 + PDGFR β -TK, n=3. Scale bar: 10 μm . **E** *Twist* transcript levels in 4T1 tumors from WT, PDGFR β -TK and anti-ANG2 + PDGFR β -TK mice (n=4 in each group). The control group (WT) was arbitrarily set to 1, unpaired one-tailed t-test. **F** Representative images of tumors immunolabeled for LYVE-1 in the indicated experimental groups and quantification of the percent LYVE-1 $^+$ area per field of view. WT, n=3; PDGFR β -TK, n=3; anti-ANG2 + PDGFR β -TK, n=3. Scale bar: 100 μm . **G** Representative images of tumors immunolabeled for TIE2 and CD31 in the indicated experimental groups and quantification of the relative percentage of TIE2 $^+$ CD31 $^+$ vessels per visual field. WT, n=3; PDGFR β -TK, n=3; anti-ANG2 + PDGFR β -TK, n=3. Scale bar: 50 μm . **H** Representative images of tumors immunolabeled for TIE2 and CD45 in the indicated experimental groups and quantification of the relative percentage of TIE2 $^+$ CD45 $^+$ macrophages per visual field. WT, n=3; PDGFR β -TK, n=3; anti-ANG2 + PDGFR β -TK, n=3. Scale bar: 50 μm . Data are represented as the mean +/- SEM. Unless otherwise noted, one-way ANOVA with Tukey post-hoc analysis was used to determine statistical significance. * p<0.05, ** p<0.01, *** p< 0.001, ****p < 0.0001. ns: not significant.

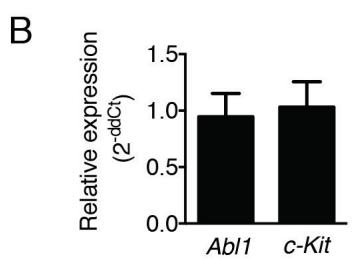
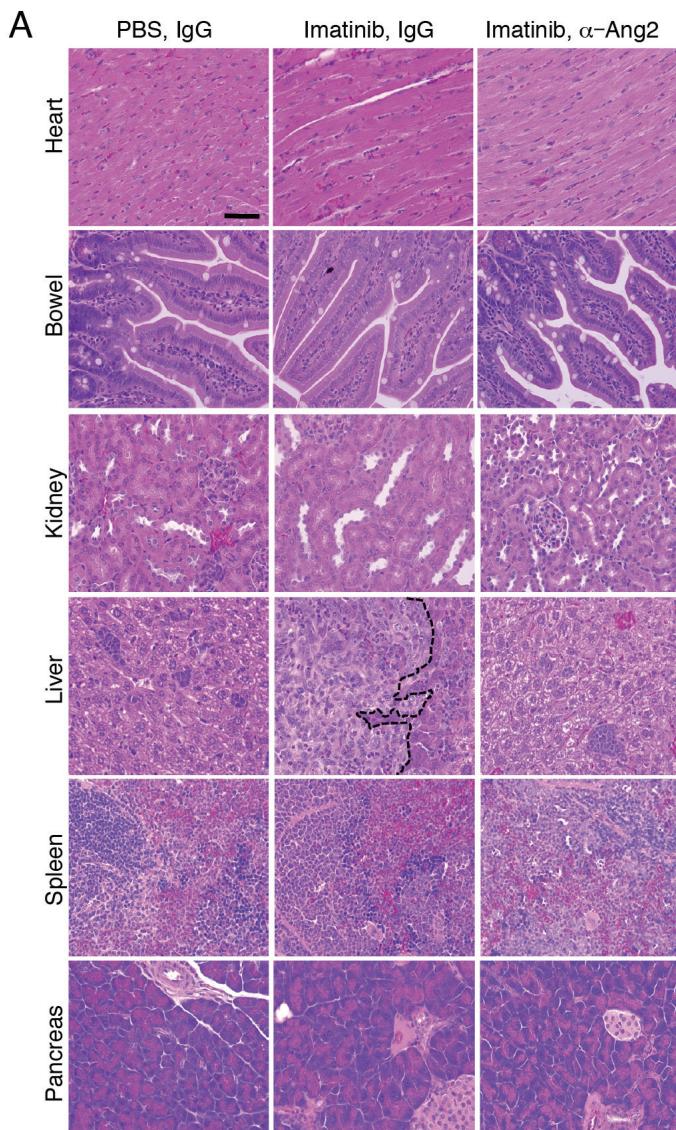


Figure S5. Imatinib and Anti-Ang2 antibody treatments present limited off target side effects, related to Figure 6.

A Representative H&E stained organs in the indicated experimental groups. A liver metastasis is delineated with a black dotted line. Scale bar: 50 μm . **B** Transcript levels of the indicated genes in 4T1 tumors from mice treated with Imatinib relative to control (PBS treated) mice. n=5 for each group, the control group (WT) was arbitrarily set to 1, and unpaired one-tailed t-test was used. Data are represented as the mean +/- SEM.

Supplementary Table**Table S1. Primer sequences used in this study, related to Figure 3.**

Vegfa-qrtF	GCACATAGAGAGAATGAGCTTCC
Vegfa-qrtR	CTCCGCTCTGAACAAGGCT
Vegfc-qrtF	GAGGTCAAGGCTTTGAAGGC
Vegfc-qrtR	CTGTCCTGGTATTGAGGGTGG
COL1A1-qrtF	GCTCCTCTTAGGGGCCACT
COL1A1-qrtR	CCACGTCTCACCATGGGGG
COL6A2-qrtF	AAGGCCCATGGATTCCC
COL6A2-qrtR	CTCCCTCCGACCATCCGAT
MMP12-qrtF	GAGTCCAGGCCACCAACATTAC
MMP12-qrtR	GCGAAGTGGGTCAAAGACAG
Dkk3-qrtF	TCAGGAGGAAGCTACGCTCAA
Dkk3-qrtR	GTTCACCTCAGAGGACGTTTAG
CXCL1-qrtF	CAGGGTCAAGGCAAGCCTC
CXCL1-qrtR	CTGGGATTCACCTCAAGAACATC
CXCL9-qrtF	TCCTTTGGGCATCATCTTCC
CXCL9-qrtR	TTTGTAGTGGATCGTGCCTCG
Ang1-qrtF	CACATAGGGTGCAGCAACCA
Ang1-qrtR	CGTCGTGTTCTGGAAGAAATGA
Ang2-qrtF	AGCAGATTGGATCAGACCAG
Ang2-qrtR	GCTCCTCATGGACTGTAGCTG
Wnt10a-qrtF	CCTGTTCTCCTACTGCTGCTGG
Wnt10a-qrtR	CGATCTGGATGCCCTGGATAGC
Notch4-qrtF	CTCTGCCACTCAATTCCCT
Notch4-qrtR	TTGCAGAGTTGGGTATCCCTG
CXCR4-qrtF	GACTGGCATAGTCGGCAATG
CXCR4-qrtR	AGAAGGGAGTGTGATGACAAA
c-Kit-qrtF	GCCACGTCTCACCATCTG
c-Kit-qrtR	GTCGGGATCAATGCACGTCA
Abl1-qrtF	AAGGGGCTCTTCGTCCCTC
Abl1-qrtR	AGAGTGCCACAAAAAGGTTGG
Twist-qrtF	CTGCCCTCGGACAAGCTG
Twist-qrtR	CTAGTGGGACGCGGACAT
ARP/36B4-qrtF	GGAGCCAGCGAGGCCACACTGCTG
ARP/36B4-qrtR	CTGGCCACGTTGCGGACACCCCTCC
GAPDH-qrtF	AGGTGGTGTGAACGGATTG
GAPDH-qrtR	TGTAGACCATGTAGTTGAGGTCA

Supplemental Experimental Procedures

4T1 orthotopic and intravenous mammary cancer model and agent administration

PDGFR β -TK or littermate control female mice, between the ages of 6 and 12 weeks, were used for orthotopic implantation of 4T1 mammary epithelial cancer cells (0.5×10^6 in each breast pad). Data from a subset of the PDGFR β -TK mice in the late pericyte depletion experiments shown in Figure 1 was reported in our previous studies (Cooke et al., 2012). Ganciclovir (GCV, Invivogen) treatments were initiated once the average tumor burden reached 500 mm^3 for the late depletion group and before the average total tumor burden reached 100 mm^3 for the early depletion group. Mice received daily intraperitoneal (i.p.) GCV injections at a 50 mg/kg body weight (BW) dose. Tumor volumes were measured every 2-3 days using Vernier calipers and volumes were calculated using the formula (length x width² x $\pi/6$). Mice were euthanized when the tumor size of control mice reached approximately $2,500 \text{ mm}^3$. Mice also received i.p. injections of the neutralizing anti-ANG2 antibody (LC06, Roche Diagnostics) or control isotype matched IgG antibody once a week (10 mg/kg BW in 0.2 ml PBS) (Thomas et al., 2013), or imatinib or PBS by oral gavage daily (50 mg/kg BW in 0.1 ml). For intravenous injection, 0.5×10^6 4T1 cells were injected in the retro-orbital venous plexus and mice euthanized 7 days post cancer cell injection. In this setting, GCV injections were initiated 3 days before cancer cell injection. Mice were also injected i.p. with a single dose of hypoxyprobe (60 mg/kg BW in 0.5 ml of pimonidazole, HPI Inc.) 30 minutes before euthanasia.

Newborn mice treatment for retina experiments

PDGFR β -TK or littermate control newborn mice were treated with GCV dissolved in PBS from P0 to P5 (early treatment) or P4 to P9 (late treatment). Ganciclovir (50 mg/kg BW in 10 μ l) was

administered by i.p. injection daily for 5 consecutive days. Under anesthesia, 100 µl of 10mg/ml FITC-dextran (2,000 kDa or 70 kDa, Sigma) was injected intracardially and allowed to circulate for 5 minutes. The pups were euthanized by decapitation and the retinas as well as other organs were collected for further analysis. PDGFR β -TK pups were also treated with anti-ANG2 or control anti-IgG antibodies in combination with GCV. Anti-ANG2 or anti-IgG was administered intraperitoneally once at P4 (10 mg/kg BW, at a volume of 10 µl) and GCV (50 mg/kg, at a volume of 10 µl) was administered daily by intraperitoneal injection until sacrifice (P9).

Quantification of metastatic burden and tumor necrosis

Hematoxylin and eosin staining of lung sections from paraffin-embedded tissue was generated by the BIDMC and MDACC histology core facilities. Image of an entire lobe of the lung was obtained using the Aperio Slide Scanner. Metastases were identified via histopathological analysis based on H&E staining and metastatic area was quantified by NIH ImageJ software as a percentage of total lung area. High magnification images (original magnification x100 or x90) of the metastatic area are provided for each lung photomicrographs. Tumor necrosis was assayed on Hematoxylin counter stained whole tumor cross-section and quantified by NIH ImageJ software as a percentage of total tumor area.

Immunostaining

Harvested tumors and lungs were fixed in 10% neutral buffered formalin, dehydrated, and embedded in paraffin. For hypoxyprobe immunohistochemistry, the deparaffinized tumor sections were incubated in 10 mM citrate buffer (pH 6.0) for 1 hour at boiling temperature prior to blocking with M.O.M. Mouse IgG Blocking Reagent (Vector Laboratories, West Grove, PA)

for 1 hour. Sections were incubated with HypoxyprobeTM antibody (1:50, HPI Inc.) overnight at 4°C, followed by incubation with biotin-conjugated anti-rabbit/rat/mouse IgG and ABC reagent (Vector Laboratories, West Grove, PA) for 30 min each at room temperature. The sections were then developed by DAB staining according to the manufacturer's instructions. Images were obtained by either light microscopy at 4X magnification or the Aperio Slide Scanner. DAB (brown) positivity was analyzed in ≥3 fields/tumor by NIH ImageJ analysis software at an original magnification of X4 or on scanned tumor images. Control and treated mice within an experimental set (3 or more tumors/group) were analyzed and results reported as staining area per tumor section or percent staining per visual field (4X). Alternatively, harvested tumors and lungs were embedded in O.C.T. medium (TissueTek, Torrance, CA), and immunostainings were performed on frozen sections. Frozen sections were fixed in either 4% PFA for 5 minutes or acetone for 10 minutes at 4°C and blocked one hour with 5% donkey or goat serum in PBST at room temperature. Following blocking, sections were incubated in 1:50 rat anti-PDGFRβ (eBiosciences), 1:200 rabbit anti-NG2 (Millipore), 1:300 desmin, 1:100 CD31 (DSHB), 1:100 CD31 (BD Pharmingen), 1:200 Collagen IV (MP Biomedicals), 1:50 CK8 (DSHB), 1:200 αSMA (Sigma), 1:100 ZO-1 (Invitrogen), 1:100 FITC (AbD Serotec), 1:200 LYVE-1 (AngioBio), 1:100 Vimentin (Cell Signaling), at 4°C overnight, followed by fluorescent secondary antibodies. Slides were mounted with either DAPI, DRAQ5 (Molecular Probe), or Sytox Green staining, to label the nuclei. For Figure S4G-H, 1:50 PE-conjugated anti-TIE2 (eBiosciences) was used with Tyramide Signal Amplification (TSA) Systems (PerkinElmer), followed by immunoableing with 1:50 FITC-conjugated anti-CD31 (BD Pharmingen) or 1:100 APC-conjugated anti-CD45 (BD Pharmingen). Positive staining was quantified in ≥3 visual fields/tumor at original magnification x20, x40 or x63 using NIH ImageJ software, where the

same threshold was used for all compared conditions to determine the positive staining area fractions per field. Three to eight tumors/group were used in the assessments. For data presented in Figure 1C & H-I, the WT group contained WT mice treated with GCV early and late. Statistical analysis was done using the average staining area fraction per tumor. Stainings were visualized on either the Zeiss Axioskop 2 microscope or the Zeiss LSM 510 Meta Confocal microscope. Quantification of the number of PDGFR β^+ /NG2 $^+$ double-positive cells (4 fields/tumor and 4 mice/group) was performed by NIH-ImageJ cell counter application and reported as percent co-localization per visual field. The number of pericytes that are associated with vessels were determined by ImageJ cell counter application under original magnification x40 and reported as percentage of vessels that have associated pericytes out of the total number of vessels, per visual field. Percent pericyte coverage was determined by the following formula: Number of pericyte-associated CD31 $^+$ vessels/field divided by the total number of CD31 $^+$ vessels/field multiplied by 100. Quantification of the relative percentage of TIE2 $^+$ CD31 $^+$ vessels and TIE2 $^+$ /CD45 $^+$ macrophages (6 fields/tumor and 3 mice/group) was performed by NIH-ImageJ and reported as relative percent co-localization over total CD31 or CD45 positive area per visual field.

In situ hybridization

In situ hybridization (ISH) was performed on frozen 4T1 tumor sections using standard methods. Briefly, frozen tumor sections (4-6 tumors/group) were cut into 10 μ m-thick sections using a cryostat (Leica), post-fixed in 4% PFA, acetylated in 1% triethanolamine and 0.25% acetic anhydride, pre-hybridized, then hybridized with *ANG2* probe overnight at 65°C. After hybridization, sections were washed and incubated with AP-conjugated sheep anti-DIG antibody

(1:1000; Roche) for 90 min at room temperature. After three washes, sections were incubated in BM Purple (Roche) until positive staining was seen. Digoxigenin labeled *ANG2* *in situ* riboprobes were generated by *in vitro* transcription method (Promega and Roche). ANG2 plasmid construct for generating the probes was provided by Anne Eichmann (Yale University School of Medicine). Immunostaining for Collagen IV and CD31 was performed after this step, as previously described. Images were obtained at x20 magnification. Quantification for *ANG2* signal was performed by NIH ImageJ software, where the same threshold was used for all compared conditions to determine the positive staining area fractions per field. The results reported as positive staining area fraction per field.

Immunohistochemistry of whole-mount retinas

Eyes harvested from the pups were prefixed in 4% paraformaldehyde (PFA) for 10 min at room temperature. Retinas dissected in PBS were post-fixed in 4% PFA overnight at 4°C. Permeabilization of retinas were done in PBS, 0.5% Triton X-100, and 1% normal goat serum overnight at 4°C. After blocking in blocking buffer (PBS, 0.5% Triton X-100, 10% normal goat serum) for 1 hr at room temperature, retinas were incubated with primary antibody (NG2, PDGFR β , Collagen IV and CD31, as described above) in blocking buffer overnight at 4°C. After washing in PBS/0.5% Triton X-100 for 2–3 hrs, retinas were incubated in Alexa Fluor-conjugated secondary antibody then washed several times. Retinas were then washed twice in PBlec (PBS at pH 6.8, 1% Triton X-100, 0.1 mM CaCl₂, 0.1 mM MgCl₂, 0.1 mM MnCl₂) and incubated in Isolectin B4 (1:500; I21411, Molecular Probes) in PBlec overnight at 4°C. The retinas were flat-mounted using ProLong Gold/DAPI anti-fade reagent (P36935, Molecular Probes), following a wash in PBS and a brief post-fixation in PFA. Flat-mounted retinas were

analyzed by fluorescence microscopy using a Nikon Eclipse 80i or Zeiss Axioskop 2 microscope equipped with a Nikon DS-2 digital camera or by confocal laser-scanning microscopy using a Zeiss LSM 510 META. Images were processed using Adobe Photoshop and ImageJ software.

Analysis of postnatal retinal angiogenesis

Images of whole mount retinas were taken at 10x magnification to measure vessel density. The number of branch points per field (100 X 100 μm fields, images taken with 10X magnification, 3 fields/retina and 3-4 retinas/group) at the periphery of vasculature was quantified using Image J. FITC-dextran was visualized directly by fluorescent microscopy under the green fluorescent filter and quantified by ImageJ area fraction analysis. 3-8 fields/retina and 3-4 retinas / group were analyzed at original magnification x10. Vessel diameter was measured at original magnification x63 and 8-10 fields/ retina and 3-4 retinas / group was analyzed.

ELISA

Tumors were lysed in 300-600 μl of PBS supplemented with proteinase inhibitors (Roche) on ice. The lysate was then subjected to 2 freeze-thaw cycles then spun for 15 min at 5000 rpm at 4°C. The lysate was cleared with a second centrifugation for 15 min at 10,000 rpm at 4°C. The protein lysate was quantified using the BCA protein assay reagents (Pierce), accordingly to manufacturer's directions. 50 μg of lysates was diluted in the sample diluent buffer provided in the Angiopoietin-2 Mouse ELISA Kit (Abcam) and the ELISA was then carried out following the manufacturer's directions.

Microarray analysis and quantitative PCR analyses

Total RNA was isolated from 4T1 tumors implanted in WT+GCV late (n=4) and PDGFR β -TK+GCV late mice (n=4) or WT+GCV early (n=8) and PDGFR β -TK+GCV early mice (n=8) using RNeasy Plus Mini Kit (Qiagen), and equal amount of RNA from each tumors in each group was pooled together, and submitted to the Molecular Genetics Core Facility at Children's Hospital (Boston, MA). Microarray analysis was performed using Mouse Ref8 Gene Expression BeadChip (Illumina), and gene expression was determined by MetaCore (GeneGo) and Genome Studio (Illumina) software. Ingenuity Pathway Analysis (IPA) was performed on the microarray data set, with a threshold of 1.2 fold. Total RNA was also isolated from 4T1 tumors implanted in WT mice treated with GCV and anti-IgG (n=3), PDGFR β -TK mice treated with GCV and anti-IgG mice (n=3), and PDGFR β -TK mice treated with GCV and anti-ANG2 antibody (n=3) using RNeasy Plus Mini Kit (Qiagen) and submitted to the Molecular Genetics Core Facility at MDACC. Gene expression analysis was performed using Mouse Ref6 Gene Expression BeadChip (Illumina), and the Limma package from R Bioconductor (Gyorffy et al., 2012) was used to analyze differentially expressed genes. Pathway analysis was performed using Ingenuity Pathway Analysis (IPA). All microarray data were deposited in Gene Expression Omnibus under the accession number GSE55785. For RT PCR analyses, tumor or retina tissue samples were homogenized in Trizol® (Invitrogen) and RNA was extracted according to manufacturer's instructions. cDNA was generated using the High Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems). Gene Expression was determined using the Applied Biosystems 7300 Sequence Detector System and SYBR green as the fluorescence reporter. Measurements were standardized to the housekeeping genes (ARP/36B4 or GAPDH). Primer sequence information is listed in Table S1.

Kaplan-Meier plotter analyses (Gyorffy et al., 2012)

The *Angpt1* Affymetrix ID 205608_s_at, *Angpt2* Affymetrix ID 211148_s_at, and *Pdgfrb* Affymetrix ID 202273_at were used as selected probe set for analysis of 3455 patient transcriptome with known recurrence free survival (the 2014 version of the database was used). Patients were split by median expression and selection criteria was not further restricted by subtypes or treatment. Both hazard ratio (HR) and Log-Rank test P value are listed.

Supplemental References

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